AstraZeneca

SH-TPA-0003

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Exanta™

ACTIVE INGREDIENT: Ximelagatran

Trial title (number): Efficacy and Safety Study of the Oral Direct Thrombin Inhibitor Ximelagatran Compared with Dose-Adjusted Warfarin in the Prevention of Stroke and Systemic Embolic Events in Patients with Atrial Fibrillation (SPORTIF III)

Developmental phase: Therapeutic confirmatory (III)
First subject recruited: 25 July 2000
Last subject completed: 30 September 2002
Approval date: 26 September 2003

OBJECTIVES

Primary

To determine whether the efficacy of ximelagatran is non-inferior to that of dose-adjusted warfarin, aiming for an International Normalised Ratio (INR) of 2.0 - 3.0, for the prevention of all strokes (fatal and non-fatal) and systemic embolic events (SEE) in patients with chronic nonvalvular atrial fibrillation.

It was a prerequisite that, for the non-inferiority to be formally addressed, the effectiveness of ximelagatran over placebo (utilising a previous meta-analysis of warfarin over placebo) was established.

Secondary and tertiary

To compare the efficacy of ximelagatran to that of dose-adjusted warfarin, aiming for an INR 2.0 - 3.0:

- for the combined endpoint of prevention of death, non-fatal strokes, non-fatal SEE and non-fatal acute myocardial infarction (AMI).
- for the combined endpoint of prevention of ischaemic strokes, transient ischaemic attacks (TIAs) and SEE.
- for the prevention of all strokes with a poor outcome (defined as a Modified Rankin score of≥3 or a Barthel score of <60, at 3 months post-stroke).
- for the prevention of all strokes and SEE in patients≥75 years of age with nonvalvular atrial fibrillation and to compare this with patients below the age of 75 years.

To assess the safety of ximelagatran compared to dose-adjusted warfarin, aiming for an INR 2.0 - 3.0, with an emphasis on major and minor bleeding events and treatment discontinuations.
To measure the time and travelling costs associated with the measurement of INR while on warfarin. (The health economic data were country-specific and collected from patients in Australia, France, Portugal, Spain, Sweden, and the UK, who were randomised to warfarin.)

METHODS

Study design

This was a randomised, open-label, parallel-group study. Primary endpoint assessment was first performed by a local neurologist or stroke physician unaware of the patient's medication. A blinded Clinical Event Adjudication Committee (CEAC) performed all endpoint adjudications. Patients with chronic nonvalvular atrial fibrillation (AF) were stratified according to aspirin use, previous stroke or TIA, and country.

Target patient population and sample size

It was planned that approximately 3000 eligible patients would be randomised. Eligible patients were to be at least 18 years of age, with evidence of chronic AF (persistent or paroxysmal) verified by at least 2 ECGs in the previous year, the second ECG being obtained within 2 weeks before randomisation. Patients were also to have at least one of the following risk factors for stroke: previous stroke, TIA or SEE; hypertension; left ventricular dysfunction; aged ≥75 years; aged≥65 years with either coronary artery disease or diabetes mellitus.

Patients who had had a stroke within 30 days, or a TIA within 3 days, of enrolment were to be excluded, together with patients who had conditions associated with an increased risk of bleeding or whose haemostatic function was compromised. Patients were also to be excluded if they had transient AF caused by reversible disorders (eg, current thyrotoxicosis, pulmonary embolism) or if cardioversion was planned. Other cardiac reasons for exclusion were atrial myxoma, left ventricular thrombus, rheumatic valve disease (including mitral stenosis and symptomatic aortic stenosis), mechanical or prosthetic heart valves, or hospitalisation for acute coronary syndromes or percutaneous coronary artery intervention within 30 days of screening. Patients were not eligible if they had a contraindication for anticoagulation (eg, endocarditis), pregnancy, liver disease, or if they had recorded drug addiction or alcohol abuse in the previous 3 years.

Concomitant treatment with antiplatelet agents, fibrinolytic agents, other anticoagulants or continuous treatment with NSAID drugs were prohibited during the study (except for certain topical NSAIDs in Japan), although aspirin ≤100 mg/day was allowed.

Elevated ALAT has been observed in 5% to 6% of patients taking ximelagatran in previous studies and so patients with persistent raised liver enzymes ≥2x the upper limit of normal were to be excluded as a precaution.

Investigational product and comparator: dosage, mode of administration and batch numbers

Ximelagatran tablets, **36 mg bid** 10 batches:
H 1384-02-01-01, H 1384-02-01-02, H 1384-02-01-03, H 1384-02-01-05, H 1384-02-01-06, H 1384-02-01-09, H 1384-02-01-10, H 1384-02-01-11, H 1384-02-01-14, H 1384-02-01-15.
Warfarin tablets, with doses titrated according to local clinical practice aiming for an INR of 2.0 - 3.0. **1 mg**: 9 batches; **2 mg**: 2 batches; **2.5 mg**: 10 batches; **3 mg**: 8 batches; **5 mg**: 18 batches; **10 mg**: 2 batches.

Duration of treatment

Minimum of 12 months and a maximum of 26 months (mean 17.4 months, median 18 months). The study was planned to continue until completion of 4000 patient years of

exposure to study drug and at least 80 primary endpoints were achieved, or a stopping rule (based entirely on safety) was met.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable: the incidence of stroke and SEE.
- Secondary variables: Efficacy – assessments of stroke and TIA; SEE; AMI; death.

Safety

Major and minor bleeds, adverse events; haematology, clinical chemistry, urinalysis and faeces analysis; ECG; blood pressure and heart rate; physical examination; treatment discontinuations.

Statistical methods

It was originally intended to address the primary objective with a life table analysis using SAS PROC LIFETEST. Instead the analysis was carried out using a comparison of proportions using patient-years in the denominator. This assumes exponentially distributed lifetimes. This change was documented in a protocol amendment prior to clean file.

The primary objective of the study was addressed with an Intention-to-Treat (ITT) approach. An absolute non-inferiority margin of 2% was defined. In this approach all randomised patients were included until study closure, irrespective of their protocol adherence and their continued participation in the study.

The ITT approach was also used for the primary endpoint analysed by age subgroup, and for analyses of stroke with a poor outcome. All other statistical analyses related to secondary and tertiary objectives, as well as all descriptive and exploratory analyses, were based on an On-Treatment (OT) approach. The OT approach included ITT patients but only their time on study drug was used for analysis. A maximum continuous interruption of up to 30 days without study drug was allowed for patients to remain in the OT analysis (except for cardioversion, for which the patient was allowed to interrupt treatment for 60 continuous days). The maximum total period of interruption was 60 days. Data were censored from the OT analysis on the 31st consecutive day or the 61st cumulative day of missed treatment.

An independent Data Safety Monitoring Board (DSMB) oversaw the safety of the patients as regards all endpoints, all SAEs, and clinical laboratory data, and formally compared the 2 treatment groups for safety regarding the following 4 outcomes:

- All-cause mortality
- All-cause mortality, all strokes and all SEE
- All strokes and all SEE
- Major bleeding events.

This evaluation was done when approximately 12.5%, 25%, 50% and 75% of the expected total number of patient years exposure was reached. Stopping rules were predefined.

All patients who took at least one dose of study medication were included in the safety population and were used in the analysis of adverse events.

RESULTS

Patient population

In total 3407 patients were randomised (1704 ximelagatran, 1703 warfarin) and were analysed for efficacy. One patient who was randomised to warfarin was given ximelagatran in error. This patient is included in the warfarin group for the efficacy analyses but in the ximelagatran group for the safety analyses. A further 10 randomised patients did not take study drug and so are excluded from the safety analyses. The safety population therefore comprised 3397 patients (1698 ximelagatran, 1699 warfarin). A total of 2903 patients (85%) completed at least 12 months' treatment, 1417 patients in the ximelagatran group (83%) and 1486 patients in the warfarin group (87%) and the number of patient years was similar in the 2 treatment groups. The proportion of patients who discontinued study drug was 18% in the ximelagatran group and 14% in the warfarin group (p=0.0034); this difference was mainly due to a protocol-mandated withdrawal of patients who had an increase in liver function tests (LFTs).

Table S1 Patient population and disposition (SPORTIF III)

		Ximelagatran	Warfarin	Total
Population				
N randomised (N planned)		1704 (1500)	1703 (1500)	3407 (3000)
Demographic characteristics				
Sex (N and % of patients)	Male	1158 (68%)	1196 (70%)	2354 (69%)
	Female	546 (32%)	507 (30%)	1053 (31%)
Age (years)	mean (SD)	70.3 (8.6)	70.1 (8.6)	70.2 (8.6)
	Range	29 to 92	37 to 90	29 to 92
Race (N and % of patients)	Caucasian	1494 (88%)	1500 (88%)	2994 (88%)
	Black	0 (0%)	3 (0%)	3 (0%)
	Oriental	201 (12%)	196 (12%)	397 (12%)
	Other	9 (1%)	4 (0%)	13 (0%)
Disposition				
N (%) of patients who	Completed	1548 (91%)	1564 (92%)	3112 (91%)
	Withdrew	156 (9%)	139 (8%)	295 (9%)
N analysed for safety[a]		1698	1699	3397
N analysed for efficacy[b] (ITT) (Patient years)		1704 (2467)	1703 (2474)	3407 (4941)
N analysed for efficacy (OT) (Patient years)		1704 (2289)	1703 (2361)	3407 (4651)

[a] Number of patients who took at least one dose of study treatment and had at least one data point after dosing

[b] Patient 4167 was randomised to warfarin but was given ximelagatran in error. This patient is included in the warfarin group for the ITT and OT analyses but in the ximelagatran group for the safety (AE) analyses.

ITT Intention-to-Treat; OT On-Treatment; N Number;

Randomised patients were predominantly Caucasian males with a mean age of 70 years (range 29 to 92 years). Most patients had persistent AF (92%), and most patients had AF of more than one year's duration (79%). Approximately 70% of patients had 2 or more risk factors for stroke. Fifty percent of patients had never smoked. Mean calculated creatinine clearance (CrCL) at enrolment was 83.1 mL/min (range 19.2 to 327.2 mL/min). At enrolment, 73% of patients were taking Vitamin K antagonists and

21% were taking aspirin. Overall, the treatment groups were comparable for demographic and baseline characteristics, and were representative of a population of patients with AF.

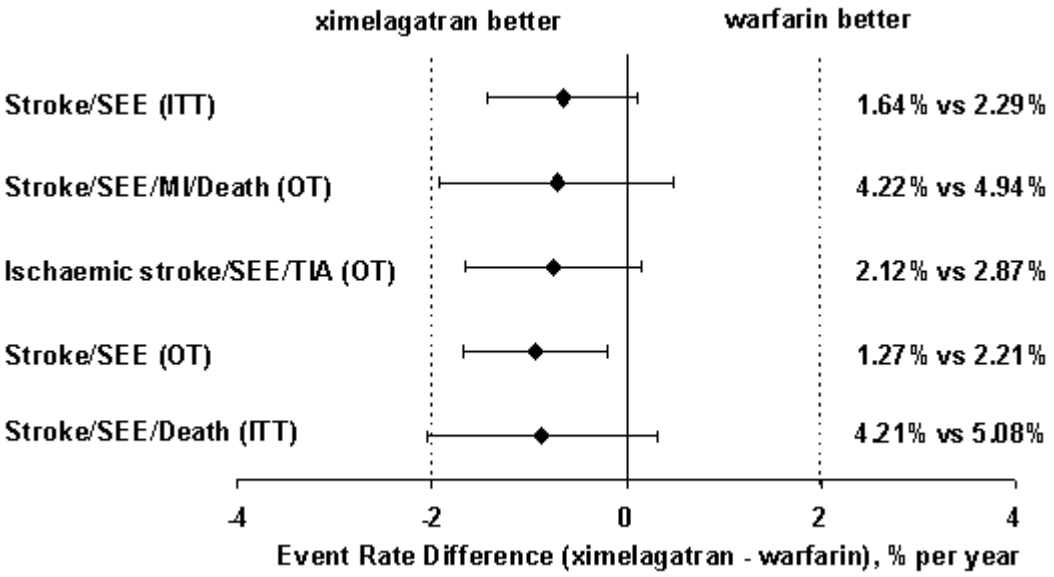
Efficacy and pharmacokinetic results

Analysis of the effectiveness of ximelagatran over placebo utilising a previous meta-analysis of warfarin over placebo gave an estimated relative risk for ximelagatran versus placebo of 0.255 (95% CI0.155 to 0.421). Analysis of the primary and secondary variables are illustrated in Figure S1.

The primary objective of establishing non-inferiority for ximelagatran in stroke/SEE prevention was met with a wide margin: 40 patients with primary events (1.64% per year) in the ximelagatran group compared with 56 (2.29% per year) in the warfarin group (p=0.100). Of these, 4 patients in the ximelagatran group and 9 patients in the warfarin group had haemorrhagic strokes; corresponding rates were 0.16% per year and 0.37% per year, respectively. The absolute risk reduction was 0.66% per year (95% CI -0.13 to 1.45%); the relative risk reduction (RRR) was 29% (95% CI -6.5% to 52%) over warfarin treatment. The primary endpoint in the OT analysis was statistically significantly in favour of ximelagatran: absolute risk reduction of 0.94% per year (95% CI 0.18 to 1.7; p=0.018); the RRR was 43% (95% CI 10% to 63%) over warfarin. Ximelagatran also demonstrated comparable efficacy to warfarin in each of the secondary endpoints.

The number of patients who had a stroke with a poor outcome was similar in the 2 treatment groups. In the sub-sets of patients 75 years and over and less than 75 years the pattern was the same with numerically fewer strokes and/or SEE in the ximelagatran group than in the warfarin group.

Figure S1 **Summary of primary and secondary efficacy variables: All CIs for between group comparisons (SPORTIF III)**



Warfarin patients were well controlled with INR within the range 2.0 to 3.0 for 66% of the time in the study and between 1.8 and 3.2 for 81% of the time; the mean INR was 2.5±0.7.

The pharmacokinetics of melagatran were predictable and in agreement with results in other patient populations. Similar plasma concentration levels were observed throughout the study period, indicating consistency over time. Melagatran clearance increased linearly with calculated CrCL, and volume of distribution with body weight. Both clearance and volume of distribution were about 20% lower in females.

Safety results

As expected, the overall incidence of adverse events was high in this study due to the severity of the underlying disease but the number of deaths, AEs and SAEs was similar in the 2 treatment groups (Table S2). There were more adverse events leading to discontinuation in the ximelagatran group, which was mainly due to the protocol-required withdrawal of patients who experienced elevations in ALAT.

Table S2 Number (%) of patients who had an adverse event in any category by study period (safety population) (SPORTIF III)

Category of adverse events	N(%) of patients who had an adverse event in each category[a]					
	Pre-treatment Ximelagatran (N=1698)	Pre-treatment Warfarin (N=1699)	Ximelagatran 36 mg bid (N=1698)	Warfarin INR 2.0-3.0 (N=1699)	Post-treatment[c] Ximelagatran (N=184)	Post-treatment[c] Warfarin (N=119)
Any adverse events	155 (9.1)	129 (7.6)	1472 (86.7)	1452 (85.5)	163 (88.6)	98 (82.4)
Serious adverse events	5 (0.3)	4 (0.2)	502 (29.6)	545 (32.1)	45 (24.5)	41 (34.5)
Serious adverse events leading to death	0	0	48 (2.8)	42 (2.5)	27 (14.7)	28 (23.5)
Serious adverse events not leading to death	5 (0.3)	4 (0.2)	474 (27.9)	525 (30.9)	23 (12.5)	16 (13.4)
Discontinuations of study treatment due to AEs	0	0	185 (10.9)	100 (5.9)	13 (7.1)	14 (11.8)
Study treatment temporarily stopped due to AE	1	1	376 (22.1)	344 (20.2)	4 (2.2)	1 (0.8)
	Total number of adverse events					
Any adverse events[b]	191	161	6422	6417	448	281
Serious adverse events[b]	5	4	769	854	58	47
Discontinuations adverse events[b]	0	0	216	119	17	15

[a] Patients with multiple events in the same category are counted only once in that category. Patientswith events in more than one category are counted once in each of those categories.

[b] Events are counted by preferred term, ie, for patients with multiple events falling under the same preferred term only one occurrence of the event is counted.

[c] The post-treatment period started the day after date of last dose of study drug.

The overall profile of AEs was consistent with the population selected by the protocol. The patients were elderly (mean age >70 years) and were followed over a long period (more than 2,400 patient years in each treatment group); therefore it was not unexpected that 85% had a least one AE. The most common AEs are shown in Table S3.

Table S3 Number (%) of patients with the most commonly reported[a] adverse events during treatment (safety population) (SPORTIF III)

Preferred term	Ximelagatran 36 mg bid (N=1698)		Warfarin INR 2.0-3.0 (N=1699)		Ximelagatran +Warfarin (N=3397)	
	N	(%)	n	(%)	n	(%)
Respiratory infection	312	(18.4)	306	(18.0)	618	(18.2)
Epistaxis	117	(6.9)	197	(11.6)	314	(9.2)
Accident and/or injury	147	(8.7)	164	(9.7)	311	(9.2)
Back pain	139	(8.2)	144	(8.5)	283	(8.3)

Preferred term	Ximelagatran 36 mg bid (N=1698)		Warfarin INR 2.0-3.0 (N=1699)		Ximelagatran +Warfarin (N=3397)	
	N	(%)	n	(%)	n	(%)
Dizziness	130	(7.7)	152	(8.9)	282	(8.3)
Dyspnoea	114	(6.7)	149	(8.8)	263	(7.7)
Purpura	120	(7.1)	130	(7.7)	250	(7.4)
Pain	113	(6.7)	123	(7.2)	236	(6.9)
Headache	113	(6.7)	110	(6.5)	223	(6.6)
Diarrhoea	112	(6.6)	106	(6.2)	218	(6.4)
Coughing	105	(6.2)	100	(5.9)	205	(6.0)
Chest pain	99	(5.8)	104	(6.1)	203	(6.0)
Oedema peripheral	94	(5.5)	109	(6.4)	203	(6.0)
Bronchitis	95	(5.6)	102	(6.0)	197	(5.8)
Infection viral	90	(5.3)	76	(4.5)	166	(4.9)
Arthralgia	77	(4.5)	87	(5.1)	164	(4.8)
Cardiac failure	69	(4.1)	93	(5.5)	162	(4.8)
Haematuria	79	(4.7)	79	(4.6)	158	(4.7)
Angina pectoris	81	(4.8)	73	(4.3)	154	(4.5)
Fatigue	80	(4.7)	67	(3.9)	147	(4.3)
Vertigo	70	(4.1)	62	(3.6)	132	(3.9)
Cerebrovascular disorder	53	(3.1)	78	(4.6)	131	(3.9)
Nausea	73	(4.3)	50	(2.9)	123	(3.6)
Hypercholesterolaemia	36	(2.1)	70	(4.1)	106	(3.1)

[a] This tables uses a cut-off of 4%. AEs are sorted by decreasing order of frequency as summarised over both treatments

Major bleeds were reported for 29 (1.7%) patients in the ximelagatran group and 41 (2.4%) patients in the warfarin group. Major and minor bleeding events in the OT analysis set were statistically significantly (p=0.007) less frequent in the ximelagatran group (25.8% per year) than in the warfarin group (29.8% per year). There was no difference between treatments with respect to the anatomical location of bleeding events.

Elevations of ALAT to >3 x ULN were noted at a higher incidence in the ximelagatran group (107 patients; 6.3%) than in the warfarin group (14 patients; 0.8%) (p<0.0001). In the ximelagatran group, 59 of the 107 patients completed the study on study drug, and ALAT values returned spontaneously to normal for 58 of these patients during the study period. Forty-eight patients discontinued study drug due to increased ALAT, which contributed to a higher rate of discontinuations in the ximelagatran group. There were numerically more myocardial infarctions in the ximelagatran group (1.7% versus 0.8% in the warfarin group), whereas congestive heart failure was less frequent in the ximelagatran-treated patients. Other reported AEs and SAEs occurred at a similar incidence in both treatment groups and were those that commonly occur in an elderly population with chronic AF, and probably were not related to the study drugs. No findings of safety concern, except those mentioned above, were observed regarding other AEs, laboratory values or physical signs.

Reference:

Albers GW, Diener HC, Grind M, Halperin JL, Horrow J, Olsson SB, Petersen P, Vahanian A, Frison L, Nevinson M, Partridge S, Executive Steering Committee on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in

patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. Lancet 2003;362(9397):1691-8.

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Exanta™ (ximelagatran) , Healthcare Professionals should view their specific country information